UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/971,338	11/17/1997	SE-JIN LEE	GDF-1	4000

7590 09/05/2003

CUSHMAN DARBY & CUSHMAN
IP PROP GRP OF PILLSBURY MADISON & SUTRO
1100 NEW YORK AVENUE
NINTH FLOOR EAST TOWER
WASHINGTON, DC 200053918

EXAMINER
ALLEN, MARIANNE P

ART UNIT	PAPER NUMBER
1631	30

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 30

Application Number: 08/971,338
Filing Date: November 17, 1997
Appellant(s): LEE, SE-JIN

Bonnie Weiss McLeod
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/21/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. The amendment after final rejection submitted 3/21/03 (amendment G, Paper No. 27) has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is deficient.

The brief asserts at page 3, lines 7-8, that the two other clones found in the library are "believed to represent allelic variations within the gene." This misrepresents the text at page 19, lines 17-29, of the specification. The specification states the "changes may represent allelic differences or they may indicate the presence of multiple GDF-1 genes."

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

In view of the entry of the amendment after final rejection submitted 3/21/03 (amendment G, Paper No. 27), claims 4 and 24 were amended and claims 34-35 were canceled.

Claims 4-10 and 22-33 are rejected under 35 USC 101 and 112 with respect to utility and how to use the claimed invention.

Claims 4-7, 22, 24-25, and 28-30 are rejected under 35 USC 112 with respect to written description. Claims 34-35 were particularly addressed with respect to new matter. Introduction of the limitations of claims 34-35 into independent claims 4 and 24 makes this rejection applicable to these independent claims and the dependent claims as indicated.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with.

The amendment after final rejection submitted 3/21/03 (amendment G, Paper No. 27) has been entered as requested.

Claims 4-10 and 22-33 stand or fall together with regard to the utility and enablement (how to use) rejections set forth under 35 USC 101 and 112.

Claims 4-7, 22, 24-25, and 28-30 stand or fall together with regard to the written description rejection set forth under 35 USC 112. It is noted that claim 33 has not been rejected under this ground of rejection. Claims 4 and 24 as well as the indicated dependent claims contain new matter and lack adequate written description.

(8) Claims Appealed

A substantially correct copy of appealed claims 9, 27, and 33 appears on pages 1, 2, and 3, respectively, of the Appendix to the appellant's brief. The minor errors are as follows: In

claim 9, line 1, "GDF- protein" should be --GDF-1 protein--. In claim 27, line 2, "figure" should be --Figure--. In claim 33, line 2, "figure" should be --Figure--.

(9) Prior Art of Record

Copies of all references are attached to this document.

Akhurst, R. J. et al. "Transforming Growth Factor Betas in Mammalian Embryogenesis," *Progress in Growth Factor Research*, Volume 2, pages 153-168, 1990.

Bengtsson, H. et al. "Potentiating Interactions Between Morphogenetic Protein and Neurotrophic Factors in Developing Neurons," *Journal of Neuroscience Research*, Volume 53, pages 559-568, 1998.

Ebendal, T. et al. "Glial Cell Line-Derived Neurotrophic Factor Stimulates Fiber Formation and Survival in Cultured Neurons From Peripheral Autonomic Ganglia," *Journal of Neuroscience Research*, Volume 40, pages 276-284, 1995.

Ebendal, T. et al. "Bone Morphogenetic Proteins and Their Receptors: Potential Functions in the Brain,"*Journal of Neuroscience Research*, Volume 51, pages 139-146, 1998.

Ernfors, P. et al. "Molecular cloning and neurotrophic activities of a protein with structural similarities to nerve growth factor: Developmental and topographical expression in the brain," *Proceedings of the National Academy of Sciences*, Volume 87, pages 5454-5458, July 1990.

Hoban, C. J. et al. "Activation of Second Messenger Pathways by GDF-1," *Society for Neuroscience Abstracts*, volume 19, page 653, Abstract 275.9, November 7-12, 1993.

Krieglstein, K. et al. "Distinct Modulatory Actions of TGF-β and LIF on Neurotrophin-Mediated Survival of Developing Sensory Neurons," *Neurochemical Research*, Volume 21, Number 7, pages 843-850, 1996.

Massague, J. "The Transforming Growth Factor -β Family," *Annual Review of Cell Biology*, Volume 6: pages 597-641, 1990.

Rankin, C. T. et al. "Regulation of left-right patterning in mice by growth/differentiation factor-1," *Nature Genetics*, Volume 24, pages 262-265, March 2000.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 4-10 and 22-33 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a either a specific, substantial, and credible utility or by a well established utility.

Claims 4-10 and 22-33 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Claims 4-10, 22-23, and 31-33 are directed to GDF-1 proteins. Claims 24-30 are directed to a process for purification of GDF-1 proteins. The protein products lack patentable utility for the reasons set forth below. Without knowing how to use the end product, the process for purification of GDF-1 proteins (claims 24-30) also lacks patentable utility.

The specification discloses using the GDF-1 proteins to make antibodies. (See specification page 12, lines 3-7.) This is not considered to be a specific asserted utility because it is generally applicable to any protein.

The specification discloses a general expectation that GDF-1 will "likely play an important role in mediating developmental decisions related to cell differentiation." (See specification page 2.) This expectation is premised upon the structural similarity of GDF-1 to members of the TGF-β superfamily. The similarities between murine GDF-1 and some TGF-β family members ranges from 26-52% in the region starting with the first conserved cysteine and extending to the C-terminus. GDF-1 is most homologous to Vg-1 and least homologous to inhibin-α. The specification also discloses that GDF-1 is not homologous outside this region to Vg-1 and acknowledges that murine GDF-1 is not the murine homolog of Vg-1. (See

specification page 20.) Note that this similarity determination is only for approximately 107 out of 357 amino acids and not for the full length amino acid sequence. (See page 19 in view of the sequence in Figure 2A-B and alignments in Figure 3A.) However, the specification fails to demonstrate or specifically associate any particular activity with GDF-1 proteins, and the specification discloses that the activities of the members of the TFG-β superfamily vary quite widely. (See specification at pages 1-2 and 12-15.) The specification states on page 12 that a potential use for GDF-1 is as a diagnostic tool as a specific marker for the presence of tumors arising from cell types that normally express GDF-1. Other disclosed potential uses are as an indicator for developmental anomalies in prenatal screens for birth defects or genetic diseases. However, no tumors are identified for any cell types that normally express GDF-1. As such, experimentation would be required to establish or reasonably confirm that it could be used as a specific marker for any tumor. Likewise, the specification does not associate GDF-1 with any birth defects or genetic diseases and experimentation would be required to establish or reasonably confirm that it could be used in this manner. Rather, the specification discloses **potential** activities and **potential** uses if one or another activity should be associated with GDF-1 when the protein is further characterized. For example, the specification at page 13, lines 16-24, states, "**Potential** uses for GDF-1 as a therapeutic tool are also suggested by the known biological activities of the other members of this superfamily. For example, since some of these proteins act as cell-specific growth inhibitors, one **potential** therapeutic use for GDF-1 is as an anti-cancer drug to inhibit the growth of tumors derived from cell types that are normally responsive to GDF-1" (emphasis added). However, the specification describes no tumors associated with GDF-1 nor any cells that are normally responsive to GDF-1. Indeed, the

following paragraphs in the specification describe "converse" or "alternative" activities. For example, the specification at page 13, lines 33-35, states, "**Conversely**, if GDF-1 functions as a growth-stimulatory factor for specific cell types, other **potential** therapeutic uses will be apparent" (emphasis added). Notice that these are diametrically opposed activities and that these uses are predicated upon further experimentation to characterize the protein. The necessity for such experimentation is stated within the specification itself at page 14, lines 29-33. "A determination of the specific clinical settings in which GDF-1 will be used as a diagnostic or as a therapeutic tool **await further characterization** of the expression patterns and biological properties of GDF-1 both under normal physiological conditions and during disease states" (emphasis added).

The claimed GDF-1 proteins are not supported by a substantial utility as the specification makes clear that further experimentation is necessary to determine and/or confirm the activity and uses of the protein. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. The specification does not inform those skilled in the art how to use the claimed invention with any particularity. The specification is required to clearly state how the claimed invention is to be used. It should be apparent to one of ordinary skill in the art how the claimed invention is to be used after reading the specification. One of ordinary skill in the art should not have to envision, infer, or "dream up" potential uses or perform undue experimentation to determine how to use the claimed invention. That is, the specification is an invitation to experiment to determine how to use GDF-1. This specification is analogous to that in Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005, which was not deemed to be enabling. "It is the specification, not the

knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research." The specification speculates on possible activities of GDF-1. None of the particular activities disclosed for other TGF-β superfamily members have been demonstrated for this protein in the specification and none were known at the time of the invention. None of the uses set forth in the specification could be practiced at the time of the invention without undue experimentation. Providing a laundry list of potential uses, some of which are diametrically opposed to each other, is not deemed to be enabling.

The relevant portion of pages 1-2 of the specification are reproduced below.

2. Background Information

A growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis have been found to be structurally homologous to transforming growth factor ß (TGF-ß). Among these are Mullerian inhibiting substance (MIS) [Cate et al, Cell 45:685-698 (1986)], which causes regression of the Mullerian duct during male sex differentiation; the bone morphogenetic proteins (BMP's) [Wozney et al, Science 242:1528-1534 (1988)], which can induce de novo cartilage and bone formation; the inhibins and activins [Mason et al, Nature 318:659-663 (1985); Forage et al, Proc. Natl. Acad. Sci., USA 83:3091-3095 (1986); Eto et al, Biochem Biophys Res Comm 142:1095-1103 (1987); and Murata et al, Proc. Natl. Acad. Sci. USA 85:2434-2438 (1988)], which regulate secretion of follicle-stimulating hormone by pituitary cells and which, in the case of the activins, can affect erythroid differentiation; the

Drosophila decapentaplegic (DPP) gene product [Padgett et al, Nature 325:81-84 (1987)], which influences dorsal-ventral specification as well as morphogenesis of the imaginal disks; the Xenopus Vg-1 gene product [Weeks et al, Cell 51:861-867 (1987)], which localizes to the vegetal pole of eggs; and Vgr-1 [Lyons et al, Proc. Natl. Acad. Sci., USA 86:4554-4558 (1989)], a gene identified on the basis of its homology to Vg-1 and shown to be expressed during mouse embryogenesis. In addition, one of the most potent mesoderm-inducing factors, XTC-MIF, also appears to be structurally related to TGF-ß [Rosa et al, Science 239:783-785 (1988); and Smith et al, Development 103:591-600 (1988)]. The TGF-ß's themselves are capable of influencing a wide variety of differentiation processes, including adipogenesis, myogenesis, chondrogenesis, hematopoiesis, and epithelial cell differentiation [Massague, J., Cell 49:437-438 (1987)], and at least one TGF-ß, namely TGF-ß2, is capable of inducing mesoderm formation in frog embryos [Rosa et al, Science 239:783-785 (1988)].

The present invention relates to a new member of the TGF-ß superfamily, and to the nucleotide sequence encoding same. This new gene and the encoded protein, like other members of this superfamily, are likely play an important role in mediating developmental decisions related to cell differentiation.

SUMMARY OF THE INVENTION

It is a general object of the present invention to provide a novel cell differentiation regulatory factor and a nucleotide sequence encoding same.

The relevant portion of pages 12-15 of the specification are reproduced below.

The TGF-β superfamily encompasses a group of proteins affecting a wide range of differentiation processes. The structural homology between GDF-1 and the known members of the TGF-β superfamily and the pattern of expression GDF-1 during embryogenesis indicate that GDF-1 is a new member of this family of growth and differentiation factors. Based on the known properties of the other members of the this superfamily, GDF-1 can be expected to possess biological properties of diagnostic and/or therapeutic benefit in a clinical setting.

For example, one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1. The availability of such markers would be invaluable for identifying primary and metastatic neoplasms of unknown origin or for monitoring the response of an identified neoplasm to a particular therapeutic regimen. In this regard, one member of this superfamily, namely, inhibin, has been shown to be useful as a marker for certain ovarian tumors [Lappohn et al, N. Engl. J. Med. 321:790 (1989)].

A second potential diagnostic use for GDF-1 is as an indicator for the presence of developmental anomalies in prenatal screens for potential birth defects. For example, abnormally high serum or amniotic fluids levels of GDF-1 may indicate the presence of structural defects in the

developing fetus. Indeed, another embryonic marker, namely, alpha fetoprotein, is currently used routinely in prenatal screens for neural tube defects [Haddow and Macri, JAMA 242:515 (1979)]. Conversely, abnormally low levels of GDF-1 may indicate the presence of developmental anomalies directly related to the tissues normally expressing GDF-1.

A third potential diagnostic use for GDF-1 is in prenatal screens for genetic diseases that either directly correlate with the expression or function of GDF-1 or are closely linked to the GDF-1 gene. Other potential diagnostic uses will become evident upon further characterization of the expression and function of GDF-1.

Potential uses for GDF-1 as a therapeutic tool are also suggested by the known biological activities of the other members of this superfamily. For example, since some of these proteins act as cell-specific growth inhibitors, one potential therapeutic use for GDF-1 is as an anti-cancer drug to inhibit the growth of tumors derived from cell types that are normally responsive to GDF-1. Indeed, one member of this superfamily, namely, Mullerian inhibiting substance, has been shown to be cytotoxic for human ovarian and endometrial tumor cells either grown in culture [Donahoe et al, Science 205:913 (1979); Fuller et al, J. Clin. Endocrinol. Metab. 54:1051 (1982)] or when transplanted into nude mice [Donahoe et al, Ann. Surg. 194:472 (1981); Fuller et al, Gynecol. Oncol. 22:135 (1984)].

Conversely, if GDF-1 functions as a growth-stimulatory factor for specific cell types, other potential therapeutic uses will be apparent. For example, one member of this superfamily, namely, activin, has been shown to function as a nerve cell

survival molecule [Schubert et al, Nature 344:868 (1990)]. If GDF-1 possesses a similar activity, as is indicated by its specific expression in the central nervous system (see below), GDF-1 will likely prove useful in vitro for maintaining neuronal cultures for eventual transplantation or in vivo for rescuing neurons following axonal injury or in disease states leading to neuronal degeneration. Alternatively, if the target cells for GDF-1 in the nervous system are the support cells, GDF-1 will likely prove to be of therapeutic benefit in the treatment of disease processes leading to demyelination.

Many of the members of this superfamily, including GDF-1, are also likely to be clinically useful for tissue repair and remodeling. For example, the remarkable capacity of the bone morphogenetic proteins to induce new bone growth [Urist et al, Science 220:680 (1983)] has suggested their utility for the treatment of bone defects caused by trauma, surgery, or degenerative diseases like osteoporosis. Indeed, the bone morphogenetic proteins have already been tested in vivo in the treatment of fractures and other skeletal defects [Glowacki et al, Lancet i:959 (1981); Ferguson et al, Clin. Orthoped. Relat. Res. 227:265 (1988); Johnson et al, Clin. Orthoped. Relat. Res. 230:257 (1988)].

A determination of the specific clinical settings in which GDF-1 will be used as a diagnostic or as a therapeutic tool await further characterization of the expression patterns and biological properties of GDF-1 both under normal physiological conditions and during disease states. Based on the wide diversity of settings in which other members of this superfamily may be used for clinical benefit, it is likely that GDF-1 and/or

antibodies directed against GDF-1, will also prove to be enormously powerful clinical tools. Potential uses for GDF-1 will almost certainly include but not be restricted to the types of clinical settings described above. Moreover, as methods for improving the delivery of drugs to specific tissues or to specific cells become available, other uses for molecules like GDF-1 will become evident.

The relevant portions of page 20 are reproduced below.

Figure 3b shows a tabulation of the percentages of identical residues between GDF-1 and the other members of the TGF-ß family in the region starting with the first conserved cysteine and extending to the C-terminus. GDF-1 is most homologous to Vg-1 (52%) and least homologous to inhibin-α (22%) and the TGF-ß's (26-30%). Two lines of reasoning indicate that GDF-1 is not the murine homolog of Vg-1. First, GDF-1 is less homologous to Vg-1 than are Vgr-1 (59%), BMP-2a(59%), and BMP-2b (57%). Second, GDF-1 does not show extensive homology with Vg-1 outside of the C-terminal portion, and it is known that other members of this family are highly conserved across species throughout the entire length of the protein [Cate et al, Cell 45:685-698 (1986); Mason et al, Nature 318:659-663 (1985); Forage et al, Proc. Natl. Acad. Sci., USA 83:3091-3095 (1986); Derynck et al, Nature 316:701-705 (1985); Mason et al, Biochem. Biophys. Res. Comm. 135:957-964 (1986); and Derynck et al, J. Biol. Chem. 261:4377-4379 (1986)]. However, GDF-1 and Vg-1 do share two regions of limited homology N-terminal to the presumed dibasic cleavage site, as shown in Figure 3c.

When read fully and in context, the specification as filed does not set forth a utility that is specific, substantial, and credible. The specification as filed discloses the necessity for further experimentation to characterize and determine how to use the GDF-1 proteins. In view of the requirement for further experimentation, no well known utility can be considered to have been known for the GDF-1 proteins at the time of the invention.

Furthermore, the specification does not enable using GDF-1 in any capacity without undue experimentation. Again, the specification is an invitation to experiment without clear direction or guidance as to the particular biological activity to investigate. Embryogenesis and mediation of cell differentiation are broad areas of basic research. No tumors nor developmental defects are identified as being associated for any screening or diagnostic methods. No normal or abnormal levels for GDF-1 are disclosed in the specification for any cell type or tissue. No direction or guidance as to particular known tumors or known developmental defects to be investigated are provided.

Claims 4-7, 22, 24-25, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection supersedes the rejection of record as set forth in the final rejection and was necessitated by the amendment to claims 4 and 24 after final rejection. Appellant was advised of the modified ground of rejection in the Advisory Action mailed 6/24/2003 (Paper No. 25).

Claims 4 and 24 were amended after final rejection to include limitations to a protein encoded by a nucleic acid that hybridizes under conditions of 65 degrees Celsius and 1 M sodium chloride to DNA having the nucleotide sequence as defined in Figure 2 or Figure 11A or 11B and remains bound when subjected to washing at 68 degrees Celsius and 0.3 M sodium chloride/ 30 mM sodium citrate (2X SSC). The specification does not disclose these limitations and as such the claims embrace new matter.

Appellant has previously pointed to page 10 and 17 of the specification for basis; however, the portion relied upon does not disclose the limitations as presently claimed.

The referenced portion of page 10 is reproduced below.

> The invention further relates to DNA segments substantially identical to the sequence shown in Figure. 2. A "substantially identical" sequence is one the complement of which hybridizes to the sequence of Figure 2 at 68°C and 1M NaCl and which remains bound when subjected to washing at 68°C with 0.1X saline/sodium citrate (SSC) (note: 20 x SSC = 3M sodium chloride/0.3 M sodium citrate).

Note that this disclosure is with respect to the sequence of Figure 2 alone and not Figure 11A or 11B and that the hybridization is at 68 degrees Celsius and not 65 degrees Celsius.

The referenced portion of page 17 is reproduced below.

> For Southern analysis, DNA was electrophoresed on 1% agarose gels, transferred to nitrocellulose, and hybridized in 1M NaCl, 50 mM sodium phosphate, pH 6.5, 2 mM EDTA, 0.5% SDS, 10X Denhardt's at 65°C. The final wash was carried out in 2X SSC at 68°C.

Note that this disclosure is in the context of a particular experimental technique and is not associated with the what was intended by the prior disclosure of "substantially identical sequences." It is not disclosed with respect to hybridization of particular sequences in the absence of electrophoresis and transfer to nitrocellulose. It is not disclosed with hybridization to the particular sequences of Figure 2 or Figure 11A or 11B. Furthermore, the claims have no limitations corresponding to 50 mM sodium phosphate, pH 6.5, 2 mM EDTA, 0.5% SDS, and 10x Denhardt's which are clearly integral to this disclosure of hybridization at 65 degrees Celsius. There is nothing that ties these two separate portions of the disclosure together to convey to one of ordinary skill in the art that the invention now claimed was originally contemplated. It is further noted that the only Southern analysis performed in the specification in Example 3 on page 22 and in Figure 5, does not identify the sequence of the probe used but it appears that it must have been from mouse and not both mouse and human as encompassed by the claims in view of the limitations to Figures 2, 11A, and 11B.

(11) Response to Argument

Appellant argues in the brief at page 7 that the predicted role of GDF-1 in embryogenesis is supported by the fact that other members of the TGF-β superfamily known at the time had a role in embryonic processes. Appellant relies upon Akhurst et al. However, Akhurst et al. discloses information about TGF-β1, TGF-β2, and TGF-β3 in mammalian embryogenesis. Akhurst et al. also discusses the wide variety of activities found in the larger TGF-β superfamily. Page 155 states, "As yet there is no definitive evidence that any of the TGFβs are endogenous regulators of mammalian embryonic processes." It is emphasized by the examiner that what is

under discussion in Akhurst et al. is TGF-β itself and not the larger superfamily. Thus, this reference provides no evidence with respect to the proteins of the larger superfamily and their role in mammalian embryogenesis. Appellant is reminded that the protein disclosed to have the highest homology to GDF-1 was not TGF-β1, TGF-β2, or TGF-β3, but rather Vg-1 which is from amphibians and not mammals. The totality of Akhurst et al. fairly indicates that those of skill in the art at the time of the invention were experimenting and looking to see whether TGF-β1, TGF-β2, and TGF-β3 proteins were involved in mammalian embryogenesis and how. The conclusion and prospects section of the reference on pages 164-165 states that the evidence would suggest that each isoform of TGF-β (i.e. TGF-β1, TGF-β2, and TGF-β3) has a distinct function *in vivo*. The reference states, "To test this proposition, it is essential that more functional studies are carried out." This supports the examiner's position that further research would be required to reasonably determine or confirm any activity or involvement of GDF-1 in embryogenesis. Furthermore, the reference amply illustrates that embryogenesis is a highly diverse and complex process including skeletal development, hematopoiesis, vascularization, and so forth. (See pages 157-164.) This is also acknowledged by the specification as filed on page 2, lines 15-20. As such, a disclosure that GDF-1 may be involved in embryogenesis cannot be considered to convey to those of ordinary skill in the art any specific or clear biological activity. It provides no direction or guidance as to which aspect or to a particular activity.

Appellant refers to the utility guidelines with respect to assignment of GDF-1 to a class of sufficiently conserved proteins that imputes the same specific, substantial, and credible utility to the assigned protein. First of all, the TGF-β superfamily has many subsets as evidenced by at least the specification and Akhurst et al. Secondly, the activities of the different members are

diverse as evidenced by at least the specification and Akhurst et al. Third, the specification fails to assert a particular biological activity within the complex and diverse activities that "embryogenesis" embraces. To the degree that appellant is relying upon the statement at page 2, lines 25-29, concerning possibly "mediating developmental decisions related to cell differentiation" rather than embryogenesis generally, this statement is not clearly limited to embryogenesis nor is it specific as to what type of mediation, what type of cells, and/or what type of differentiation. This is analogous to the fact pattern in *In re Kirk*, 153 USPQ 48, 52 in which nebulous expressions of biological activity in the specification did not convey a sufficiently explicit indication of the usefulness of the compounds and how to use them.

While appellant stresses the structural similarity of GDF-1 to members of the TGF-β superfamily, they are reminded that this similarity determination is only for approximately 107 out of 357 amino acids and not for the full length amino acid sequence. (See page 19 in view of the sequence in Figure 2A-B and alignments in Figure 3A.) They are further reminded that the specification also discloses that GDF-1 is not homologous outside this region to Vg-1. While the specification discloses that GDF-1 is most homologous to Vg-1 and least homologous to inhibin-α, no where in the specification is there an assertion that GDF-1 is expected to act similarly to a particular member of the superfamily. No where in the specification is there an assertion that GDF-1 is expected to act like the protein disclosed to have the highest similarity, Vg-1. In fact, the specification discloses that GDF-1 could have activities similar to members of the superfamily that are less structurally similar.

Appellant is reminded that the utility guidelines are just that, guidelines. They do not supersede the statutes nor the pertinent case law. In addition, the fact pattern here differs from

those set forth in the utility guidelines but closely matches the fact pattern in the pertinent case law, *In re Kirk*, 153 USPQ 48. The disclosure of the originally filed specification does not provide a specific, substantial, and credible asserted utility nor a well established utility for the claimed invention.

Appellant relies upon the Ebendal declaration previously submitted under 37 CFR 1.132. The declaration supports the examiner's position that GDF-1 activity at the time of the invention was not known, could not have been predicted, and that there was no specific or substantial utility set forth as evidenced by the degree of experimentation conducted to find an activity.

This declaration sets forth that recombinant human GDF-1 (amino acids 255-373 fused to 34 additional amino acids) was produced in E. coli and recovered as a dimer. This product potentiates human NT-3 fibre outgrowth. The assays used to establish this biological activity are referenced to Ebendal (1995) and Ernfors (1990). (Note that these references were attached to the Ebendal declaration but have not been made of record.) The declaration asserts that this biological activity on neurons is similar to other members of the TGF-β superfamily.

First of all, the particular material tested is not disclosed in the specification. That is, while Figure 11B discloses the human GDF-1 sequence, the portion of this protein and the particular fusion partner used in the declaration experiments do not appear to be disclosed in the specification. Use of the particular pRSET vector by Invitrogen does not appear to be disclosed in the specification. Use of a dimer versus a monomer does not appear to be disclosed in the specification. The fibre outgrowth assay of Ebendal et al. (1995) was developed after the effective filing date of the application. The Ernfors et al. (1990) reference is also post-filing date for the ultimate parent application (07/538,372, filed 6/15/90). Furthermore, it discloses fibre

outgrowth activity of NT-3 (although not named as such in this reference) but does not disclose similar activity of TGF-β superfamily members or GDF-1 proteins. It is noted that the declaration evidence indicates that GDF-1 alone was ineffective to evoke fibre outgrowth.

The potentiating activity between the TGF-β superfamily member OP-1 and NT-3 was not known until well after the effective filing date. (See Bengtsson et al., Journal of Neuroscience Research, 1998.) It is noted that the receptors discussed were not known at the time of the invention nor does the reference generally postulate this activity to all other members of the superfamily. The involvement of the GDF family was only determined well after the effective filing date. (See Ebendal et al., Journal of Neuroscience Research, 1998.) It was not discovered until well after the effective filing date that TGF-β3 potentiates the survival achieved with NT-3 and NT-4. (See Krieglstein et al., Neurochemical Research, 1996.)

Massague provides a review of the TGF-β superfamily at approximately the time of the invention. The reference sets forth the diverse effects of the various members of the superfamily. Notably, the potentiating effect of the Ebendal declaration is not disclosed for any member of the superfamily.

As such, the Ebendal declaration cannot be considered to demonstrate that GDF-1 possesses a function predicted by the specification. Potentiation of human NT-3 fibre outgrowth by recombinant human GDF-1 (amino acids 255-373 fused to 34 additional amino acids) produced in E. coli and recovered as a dimer was not predicted by the specification. The function established was discovered in view of further research not contemplated by the specification and using materials and techniques not available at the time of the invention.

Appellant also relies upon the Rankin et al. reference. Appellant is relying upon the filing date of the ultimate parent application, 07/538,372, filed 6/15/90. The Rankin et al. (March 2000) was published well after the effective filing date of the instant invention and the abstract itself admits that the function of GDF-1 was not known when discovered by inventor Lee. (See abstract citations 2 and 3.) It is noted that knockout mice were not routinely produced at the time of the invention. The specification does not predict that GDF-1 was involved in development of the left-right axis in mice and expression of genes expressed downstream in development. The specification does not disclose nor contemplate knockout mouse experimental models.

Like the Petrow affidavit in *In re Kirk*, 153 USPQ 48, 52, the specific biological activities discussed in the Ebendal declaration and Rankin et al. reference are absent from the specification disclosure. The Ebendal declaration and Rankin et al. reference amount to an admission that experimentation would be necessary to determine the actual uses.

Not only does the specification fail to inform one of ordinary skill in the art what to do with GDF-1, the specification cannot be considered to enable one to use GDF-1 in any of these later discovered contexts as each required experimentation well beyond the disclosure in the specification. The Ebendal declaration and Rankin et al. reference use information, materials, assays, and/or techniques that were not known at the time of the invention and thus make clear that one of ordinary skill in the art trying to determine what activity GDF-1 had at the time of the invention would have been required to go beyond routine experimentation.

It is noted that the Ebendal declaration and Rankin et al. do not speak to using GDF-1 or any other TGF-β superfamily member in prenatal screening for developmental defects in mice, humans, or any other species.

Finally, Hoban et al. (1993) establishes that even several years after the effective filing date of the invention the biological activity of GDF-1 was just being determined and assays for GDF-1 were just being developed. This abstract expressly states, "We have been working towards identifying bioassays for GDF-1." The only results disclosed are that human GDF-1 stimulates immediate early gene expression in neural cell lines. Nothing in the specification would lead one of ordinary skill in the art to this activity or use.

Appellant argues on page 12 of the brief that Figure 7 shows that GDF-1 is expressed almost exclusively in brain. This is a misrepresentation. Northern analysis demonstrated that the GDF-1 probe detected an mRNA species in adult brain, adrenal gland, ovary, and oviduct. (See page 23 and Figure 7.) The specification does not identify any tumor (brain or otherwise) associated with GDF-1 nor enable any such diagnostic or therapeutic uses.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa
July 7, 2003

Conferees

Michael P. Woodward
Irem Yucel

CUSHMAN DARBY & CUSHMAN
IP PROP GRP OF PILLSBURY MADISON & SUTRO
1100 NEW YORK AVENUE
NINTH FLOOR EAST TOWER
WASHINGTON, DC 20005-3918

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
CONFEREE